EDITORIAL

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The potential detrimental effect of corticosteroids in prostate cancer

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“...corticosteroids should be used carefully in men with prostate cancer who have been treated with androgen deprivation therapy on a long-term basis...”

Diagnosis of prostate cancer (PC) at local or regional stages is associated with an excellent prognosis [1]; however, patients with metastatic PC generally achieve only temporary disease control with hormonal therapy and they eventually develop disease progression despite castrate serum androgen levels. In the last years the number of drugs available for metastatic castration-resistant prostatic cancer (mCRPC), such as abiraterone, cabazitaxel, enzalutamide and sipuleucel-T, has rapidly increased [2]. Some of them, such as the classic chemotherapeutic docetaxel, require the concomitant use of corticosteroids. The large use of corticosteroids should lead physicians to question themselves regarding the long-term use of glucocorticoids and their role in PC and especially in advanced disease.

Corticosteroids are commonly used in the treatment of cancer due to their anti-inflammatory activities, and they have a direct effect on tumor-induced pain, secondary to bone metastases [3]. Thus, corticosteroids are used both to manage tumor-related symptoms and to counteract toxic effects and side effects associated with prostatic anticancer drugs;

they delay the onset of fluid retention induced by docetaxel [4] and they can also help to prevent the mineralocorticoid syndrome secondary to abiraterone acetate administration [5].

However, their use is not without disadvantages. The most common adverse events related to corticosteroids use are edema, hypertension, weight gain, hyperglycemia/steroid-induced diabetes, posterior subcapsular cataracts and glaucoma [6]. These toxicities depend on exposure time and total doses [7].

Furthermore, corticosteroids should be used carefully in men with PC who have been treated with androgen deprivation therapy on a long-term basis, as they could exacerbate cardiovascular risk and metabolic dysfunctions correlated with androgen deprivation therapy [8].

Recently, the androgen receptor (AR) and AR-regulated genes have been studied to be active in CRPC, despite undetectable levels of testosterone in the blood [9]. Nelson defined four states of PC based on sources of androgenic ligands and the activity of AR [10]. According to this theory, in third state, PC cells are androgen ligand independent and AR dependent. In

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this state, the AR remains active in the absence of ligands through cross-talk with other signal transduction pathways, thus corticosteroids could play a role in AR activation [10]. Preclinical evidence have enforced this theory [11] and recent studies on abiraterone acetate explain the early progression through to the promiscuous activation of AR by steroid metabolites such as glucocorticoids [12].

Richards and colleagues show that mutant L701H T877A AR is activated by exogenous glucocorticoids administered with abiraterone. Combining abiraterone with enzalutamide or increasing abiraterone doses could avoid AR promiscuous activation [13]. If this has been evaluated in preclinical studies, more confirmations to these theories come from *post hoc* analyses of two Phase III randomized and controlled trials on second-line therapies for mCRPC.

The AFFIRM trial demonstrated the efficacy of enzalutamide, an irreversible AR inhibitor, as a second-line therapy in mCRPC after docetaxel failure [14]. Analyzing demographic characteristics of the AFFIRM population, patients who received corticosteroids were generally sicker and had more advanced disease. In multivariate analysis of baseline prognostic factors, the corticosteroid use was associated with reduced survival and adverse side effects, such as the presence of visceral metastases and anemia.

Moreover, although enzalutamide showed its efficacy compared with placebo in both the noncorticosteroid- and corticosteroid-treated groups, overall survival, radiologic progression-free survival and prostate-specific antigen progression were all inferior in the corticosteroid-treated group. With regard to toxicity, patients on corticosteroids had higher rates of grade 3–4 adverse events compared with no corticosteroid patients (63.3 vs 34.4%, respectively) [15].

Similarly, in the COUAA-301 trial, which evaluated the efficacy of abiraterone after docetaxel in mCRPC [16], the role of corticosteroids at baseline was studied. Corticosteroids at baseline included prednisone, dexamethasone and other corticosteroids ($n = 489$), while 797 patients were not treated with corticosteroids. In this study, corticosteroids at baseline was not a strong independent prognostic factor in mCRPC postdocetaxel treatment, but was associated with worse baseline disease characteristics and inferior overall survival [17].

At present, we have medical options that do not need the additional use of steroids such as

enzalutamide or alpharadin. As previously stated, enzalutamide demonstrated the efficacy as a second-line therapy in CRPC in the AFFIRM trial [14]. This Phase III trial randomized 1199 men with mCRPC following chemotherapy to enzalutamide (160 mg/day) or placebo in a 2:1 ratio. Overall survival favored enzalutamide (median: 18.4 vs 13.6 months; hazard ratio for death: 0.63; 95% CI: 0.53–0.75; $p < 0.001$), which led to regulatory approval. Treatment was well tolerated and toxicities included fatigue, diarrhea and hot flashes. Seizures were reported in five patients (0.6%) receiving enzalutamide, which was expected on the grounds of previous preclinical and clinical experience, and may warrant caution when the drug is administered to patients with a history of epilepsy. Retrospective analysis from the AFFIRM trial shows that enzalutamide is active in patients with low burden disease, while it could be ineffective in the presence of multiple metastases and in highly pretreated patients [14].

Alpharadin is a calcium-mimetic radiopharmaceutical that accumulates in bones and emits α -radiation from radium-223 decay and releases relatively high energy with a narrow range (2–10 cells). Following promising results in a Phase II trial, the Phase III ALSYMPCA trial was conducted in mCRPC patients with symptomatic bone metastases, who either had received or were ineligible for docetaxel. Patients received six doses of alpharadin 50 kBq/kg intravenously every 4 weeks.

At the interim analysis, which involved 809 patients, radium-223, as compared with placebo, significantly improved overall survival (median: 14.0 vs 11.2 months; hazard ratio: 0.70; $p = 0.002$). The updated analysis involving 921 patients confirmed the radium-223 survival benefit (median: 14.9 vs 11.3 months; hazard ratio: 0.70; $p < 0.001$). Assessments of all main secondary efficacy end points also showed a benefit of radium-223 compared with placebo. Radium-223 was associated with low myelosuppression rates and fewer adverse events [18]. However radium-223 is effective only in patients with bone metastases and cannot be used in visceral or lymph node disease.

Treatment options for CRPC patients have greatly increased in recent years and several active agents can be offered to our patients [19]. To date, there are no randomized trials comparing these agents and no predictive models or biomarkers are able to identify patients who

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are likely to benefit from any of these drugs. Therefore, the choice of therapy is based on clinical expertise. Physicians should take greater account of late sequelae related to long-term corticosteroid use; a patient history should be collected and corticosteroids should be managed carefully in diabetic, hypertensive or obese patients, weighing the pros and cons of their use. Chemotherapeutic agents that require concomitant use of corticosteroids should be avoided, or it proposal of eliminating concomitant steroid use or other available medical options that do

not require the additional use of steroids, should be preferred.

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